A Stochastic Model of Pulsatile Blood Testosterone Levels

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Abstract

Mathematical methods for modeling biological processes have become increasingly important in recent decades. We will consider a mathematical model of hormone secretion in men and use it to illustrate how different areas of mathematics can contribute to the modeling process in biology.

Outline

- ⋆ Overview of the hypothalmus-pituitary-testicular axis.
- ⋆ Introduce the deterministic model.
- ⋆ Reconsider the model as a stochastic model.
- ⋆ Analysis and discussion.
- ⋆ Analogy to a harmonic oscillator with variable, nonlinear damping.
- ⋆ Conclusions and future work.

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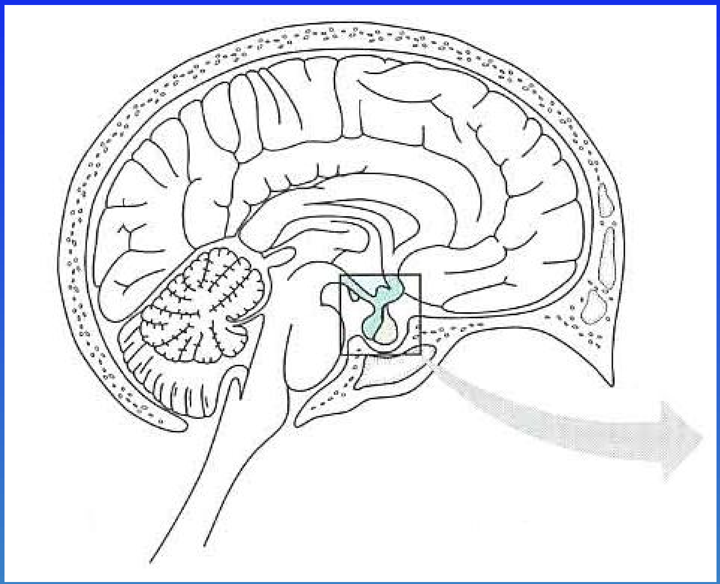
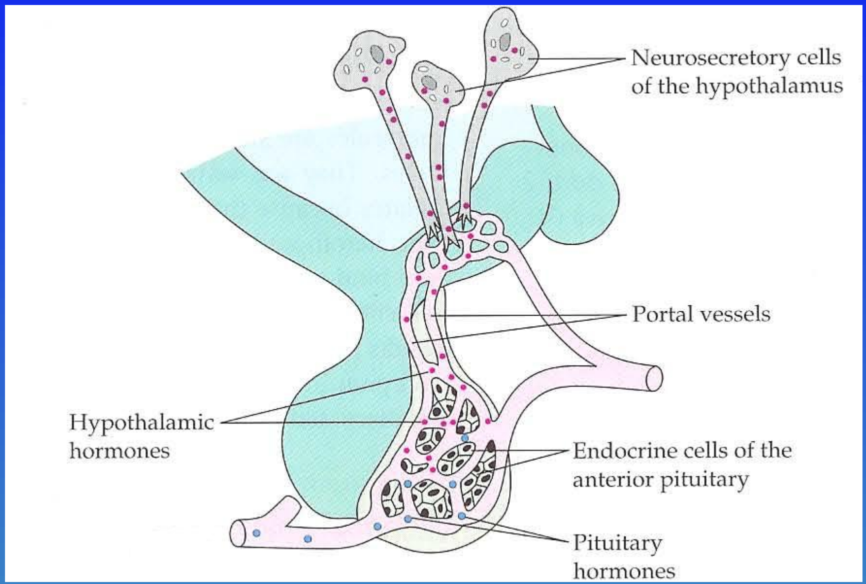
- These levels have been experimentally observed to oscillate with a period of about 2 to 3 hours.
- An imbalance can cause dramatic changes (mood, acne, and weight).
- Pathway is associated with many other important processes in the body.
- Pharmaceutical interests in chemical castration (Goserelin, Lupron, and Depo-provera) and to create a male *pill*.

The Hypothalmus-Pituitary-Testicular Axis





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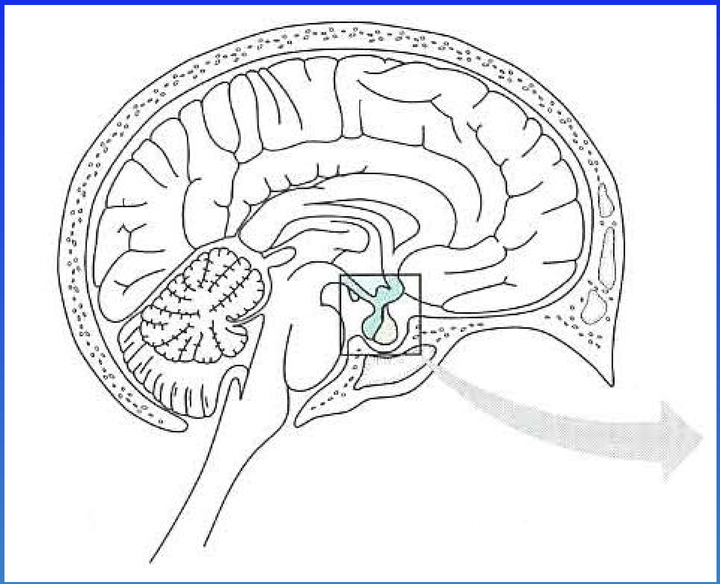
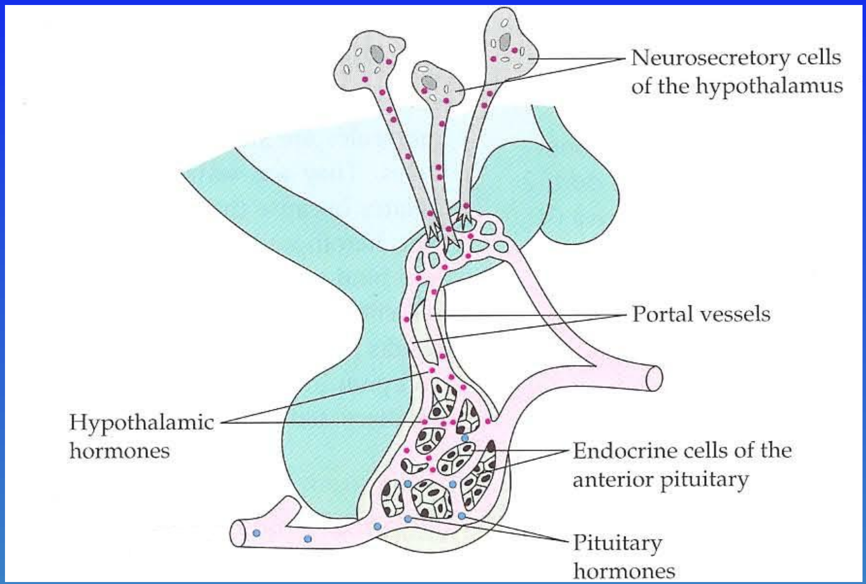
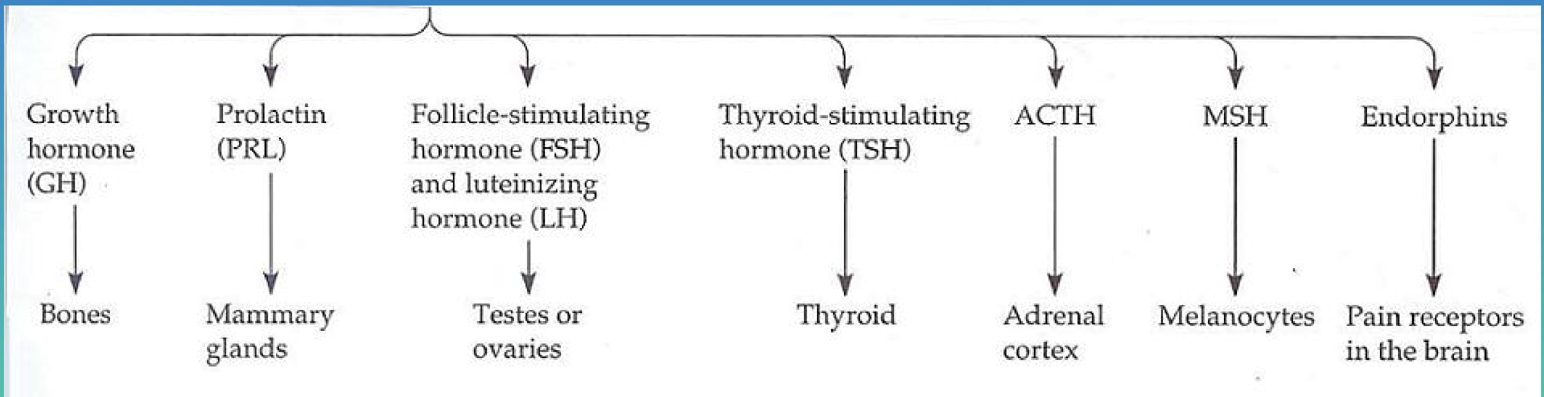
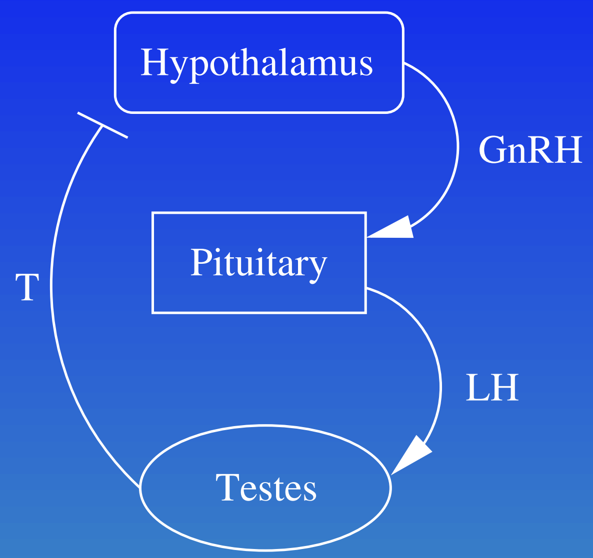






Modified from Campbell (1996).

The System

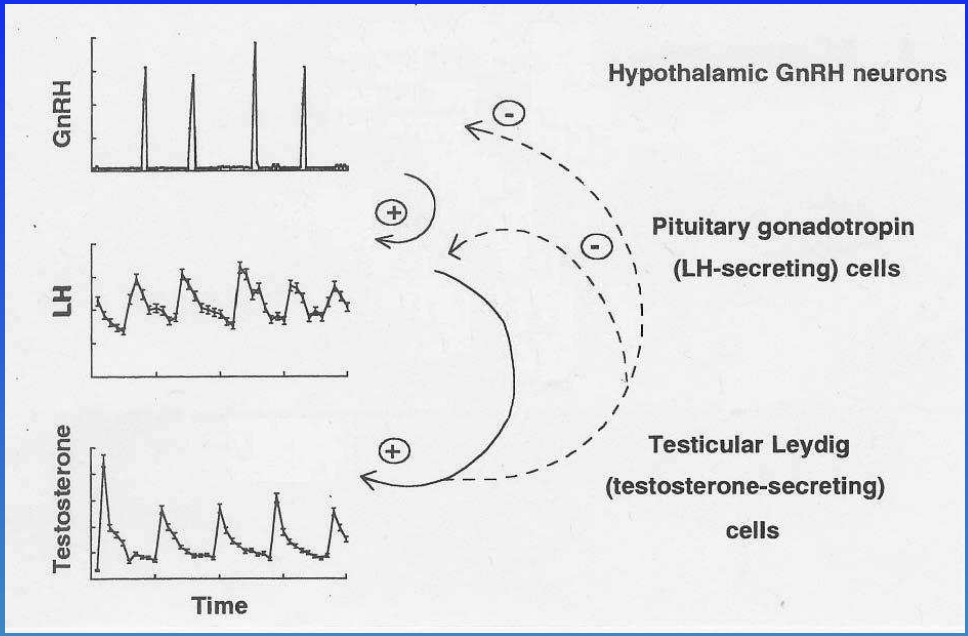


$$GnRH = \text{Gonadotropin Releasing Hormone}$$

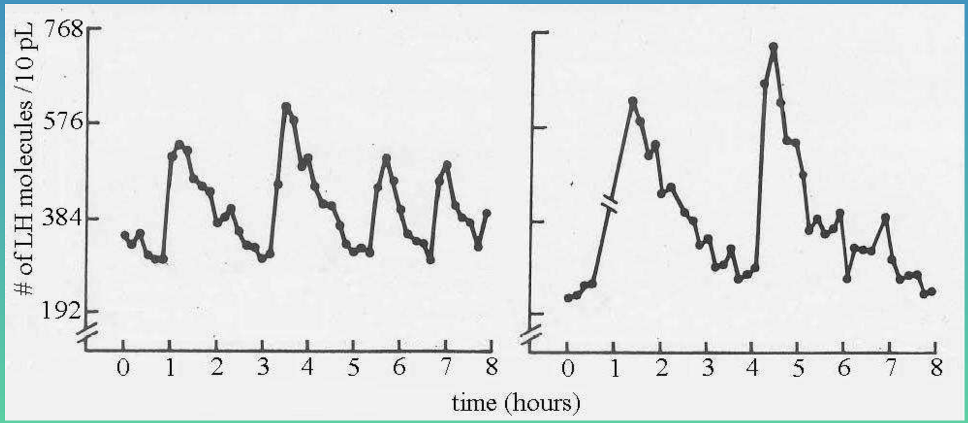
$$LH = \text{Luteinizing Hormone}$$

$$T = \text{Testosterone}$$

Experimental Observations



Modified from Yen *et al.* (1999).



Modified from Naftolin *et al.* (1973).

The Deterministic Model

If we represent the concentrations of *GnRH, LH*, and *T* by *R(t), L(t)*, and *T(t)*, respectively, then a proposed deterministic model of this system is

$$\frac{dR}{dt} = f(T) - b_1 R$$
$$\frac{dL}{dt} = g_1 R - b_2 L$$
$$\frac{dT}{dt} = g_2 L - b_3 T$$

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where

$$f(T) = \frac{A}{K + T}$$

and A, K, b_1, b_2, b_3, g_1, and g_2 are all positive constants .

History of the Model

- Goodwin (1964) first proposed the model to demonstrate oscillatory behavior in enzymatic control processes.

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- ⋆ Enciso and Sontag (2004) proved that the system has a globally stable fixed point (regardless of the length of the time-delay) and therefore does not have a limit cycle or sustained oscillations.
- ⋆ More detailed (and more complicated) models include those by Cartwright and Husain (1986) and Keenan *et al.* (1998 and 2000).

The Fixed Point

The system of differential equations has a fixed point wherever

$$R^* = \frac{1}{b_1} f(T^*)$$

$$L^* = \frac{g_1}{b_2} R^*$$

$$T^* = \frac{g_2}{b_3} L^*$$

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\end{aligned}
$$

or, plugging in the assumed form of $f(T)$ and solving, we find a positive fixed point at

$$
\begin{aligned}
R^* &= \frac{-Kb_1b_2b_3 + \sqrt{(Kb_1b_2b_3)^2 + 4b_1b_2b_3g_1g_2A}}{2b_1g_1g_2} \\
L^* &= \frac{-Kb_1b_2b_3 + \sqrt{(Kb_1b_2b_3)^2 + 4b_1b_2b_3g_1g_2A}}{2b_1b_2g_2} \\
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\end{aligned}
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Stability of the Fixed Point

LOCALLY:

The characteristic equation of the linearized system near the fixed point is

$$(\lambda + b_1)(\lambda + b_2)(\lambda + b_3) - f'(T^*)g_1 g_2 = 0$$

which only has solutions with negative real parts, i.e. $Re(\lambda) < 0$.

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SO:

The deterministic model does not have limit cycles and cannot have sustained oscillations, which was the purpose of the model! So what do we do next?

Reconsider the Physical Basis of the Problem

Take seriously the fact that events, such as the production or degradation of hormone molecules, occur in an essentially random manner. Intrinsic fluctuations play an important role when there are low numbers of molecules present.

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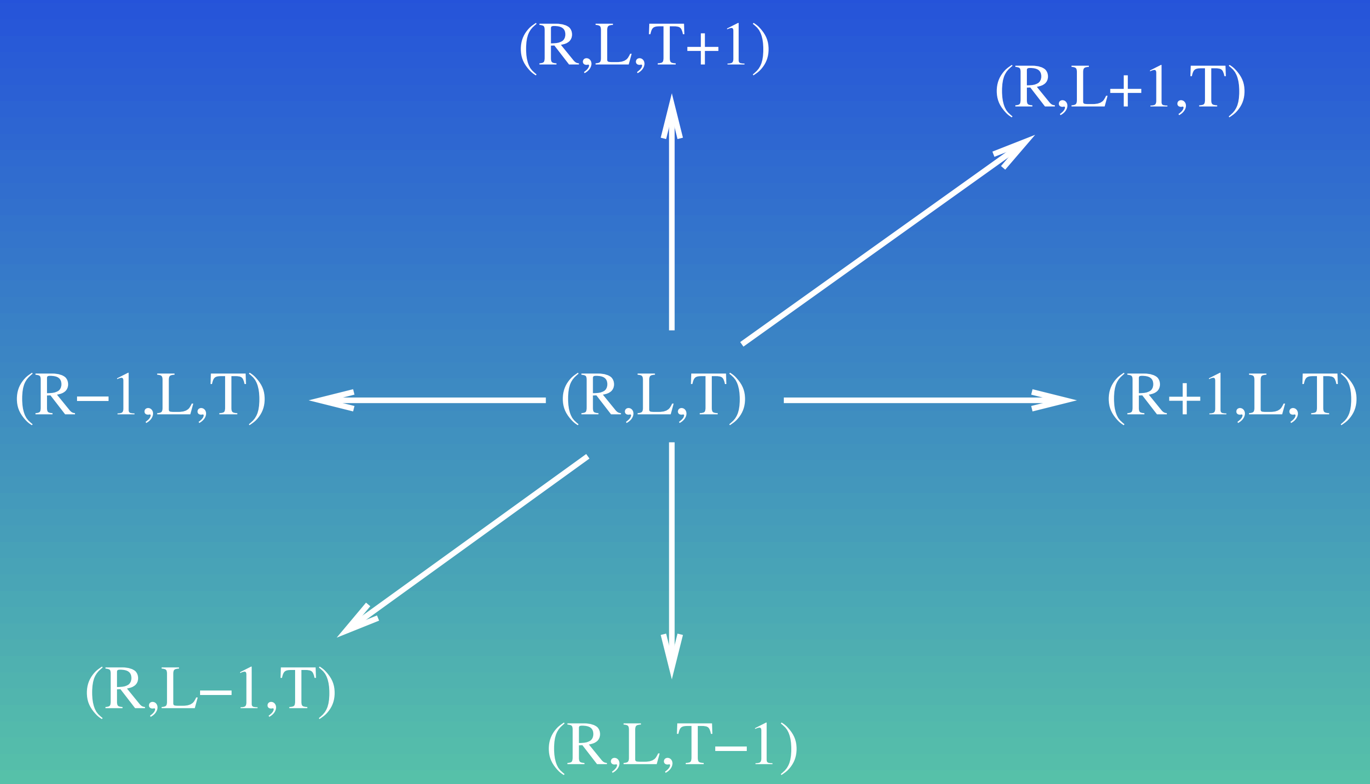

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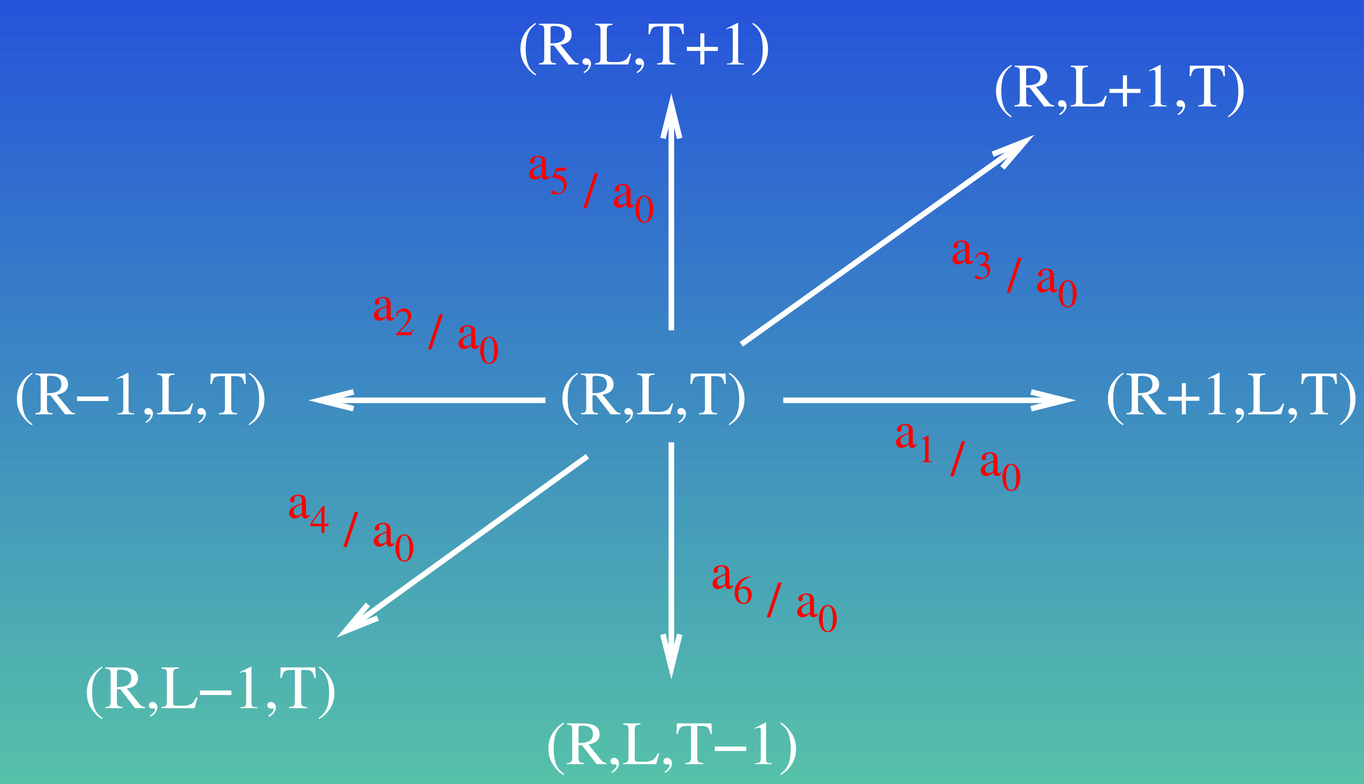

Reaction Probability Density Function

When will the next event occur and what type of event will it be?

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Define

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\begin{aligned}
P(\tau,\mu)d\tau \equiv\ & \text{probability at time } t \text{ that the next event will occur} \\
& \text{in the differential time interval } (t+\tau, t+\tau+d\tau) \\
& \text{and will be a type } \mu \text{ event,}
\end{aligned}
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where $0 \leq \tau < \infty$ and μ simply indicates what type of event occurs.

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where $0 \leq \tau < \infty$ and μ simply indicates what type of event occurs.

This joint probability distribution function can be written as

$$P(\tau,\mu)d\tau = P_0(\tau)a_\mu d\tau$$

where $P_0(\tau)$ is the probability that no event occurs in the time interval $(t, t+\tau)$ and $a_\mu d\tau$ is the probability that event μ occurs in the interval $(t+\tau, t+\tau+d\tau)$.

Density Function Cont'd...

Let

$$a_0 = \sum_{i=1}^{6} a_i$$

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from which it is easily deduced that

$$P_0(t) = e^{-a_0 t}.$$

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&= \left(\frac{a_\mu}{a_0} \right) a_0 e^{-a_0 \tau} d\tau
\end{aligned}
$$

Density Function Cont'd...

So we have

$$\begin{aligned} P(\tau,\mu)d\tau &= P_0(\tau)a_\mu d\tau \\ &= \left(\frac{a_\mu}{a_0}\right) a_0 e^{-a_0\tau} d\tau \\ &= P(\mu)P(\tau)d\tau \end{aligned}$$

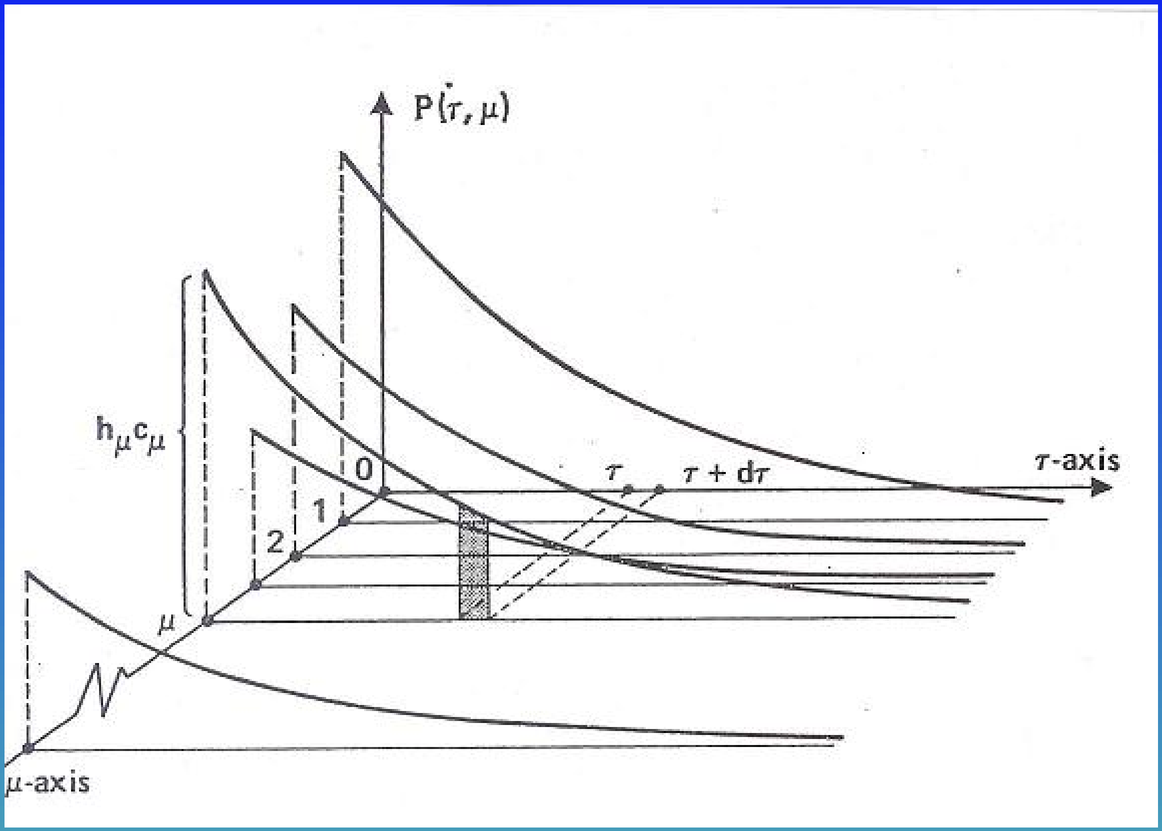
where

$$P(\mu) = \frac{a_\mu}{a_0}$$

and

$$P(\tau) = a_0 e^{-a_0\tau}.$$

Schematic of the Density Function



From Gillespie (1976).

The Probability Distribution Function

$$F(x) \equiv \int_{-\infty}^{x} P(x')dx'$$

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To generate a random value x according to a given density function $P(x)$ we need to use the inversion method, by which we simply draw a random number r from the uniform distribution in the unit interval and take x such that

$$F(x) = r \quad \text{or} \quad x = F^{-1}(r)$$

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since

$$F(x' + dx') - F(x') = F'(x')dx' = P(x')dx'.$$

Our Distribution Functions

$$P(\tau) = a_0 e^{-a_0 \tau} \quad \longrightarrow \quad F(\tau) = 1 - e^{-a_0 \tau}$$

$$P(\mu) = \frac{a_\mu}{a_0} \quad \longrightarrow \quad F(\mu) = \sum_{k=1}^{\mu} P(k)$$

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So choose r_1 and r_2 from uniform distribution in the unit interval and

$$\boxed{\begin{gathered} \tau = \frac{1}{a_0} \ln\left(\frac{1}{r_1}\right) \\ \sum_{k=1}^{\mu-1} \frac{a_k}{a_0} < r_2 \leq \sum_{k=1}^{\mu} \frac{a_k}{a_0}. \end{gathered}}$$

The Stochastic Formulation

We need to convert concentrations to numbers of molecules and reaction rate parameters to probability transition rates. For the deterministic model, we have suggested and experimentally measured values listed in the literature. A dimensional analysis shows

$$[A] = \frac{\text{mass}^2}{\text{volume}^2\text{min}} \qquad [K] = \frac{\text{mass}}{\text{volume}}$$

$$[g_1] = [g_2] = \left(\frac{\text{mass}}{\text{mass}}\right)\frac{1}{\text{min}} \qquad [b_1] = [b_2] = [b_3] = \frac{1}{\text{min}}.$$

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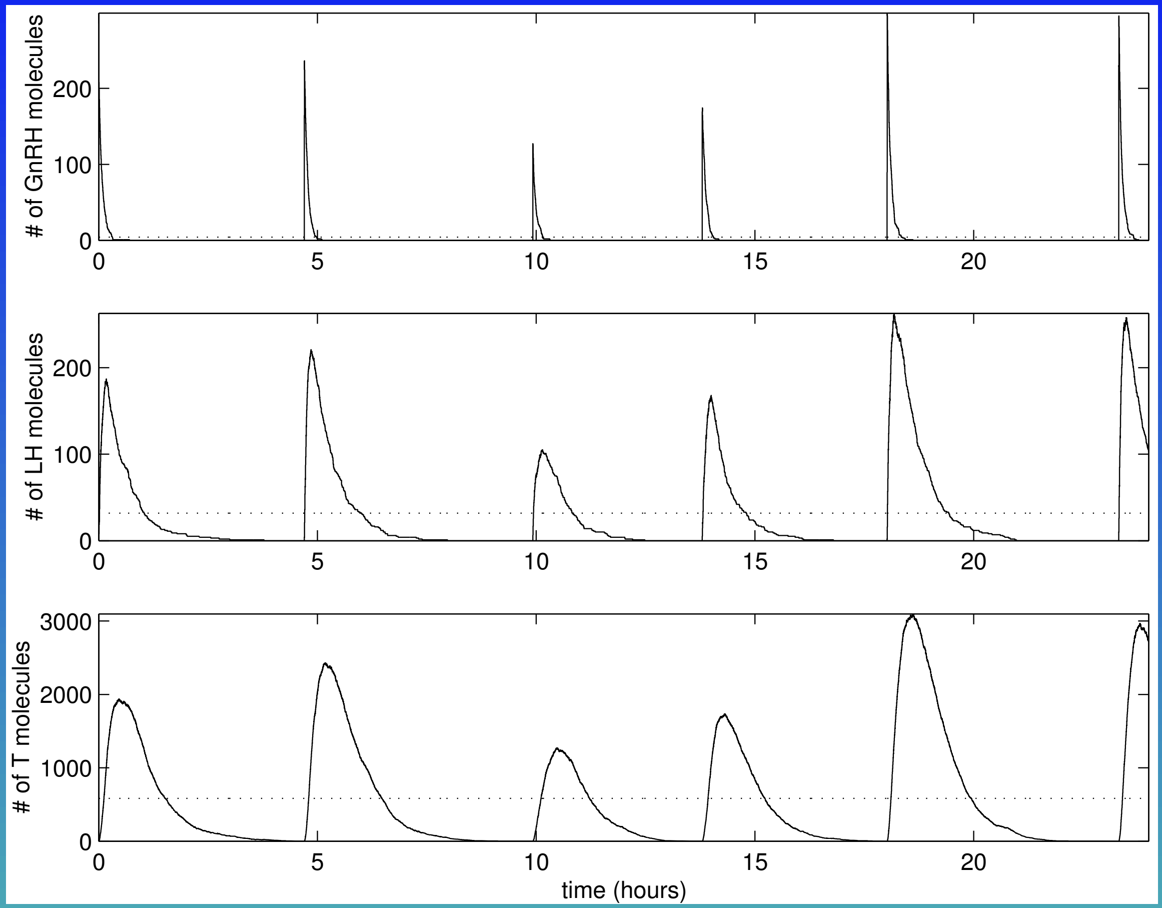
After the conversion, all we need to do is run the Gillespie algorithm with

$$a_1 = \frac{A}{K + T(t)} \qquad a_2 = b_1 R(t)$$

$$a_3 = g_1 R(t) \qquad a_4 = b_2 L(t)$$

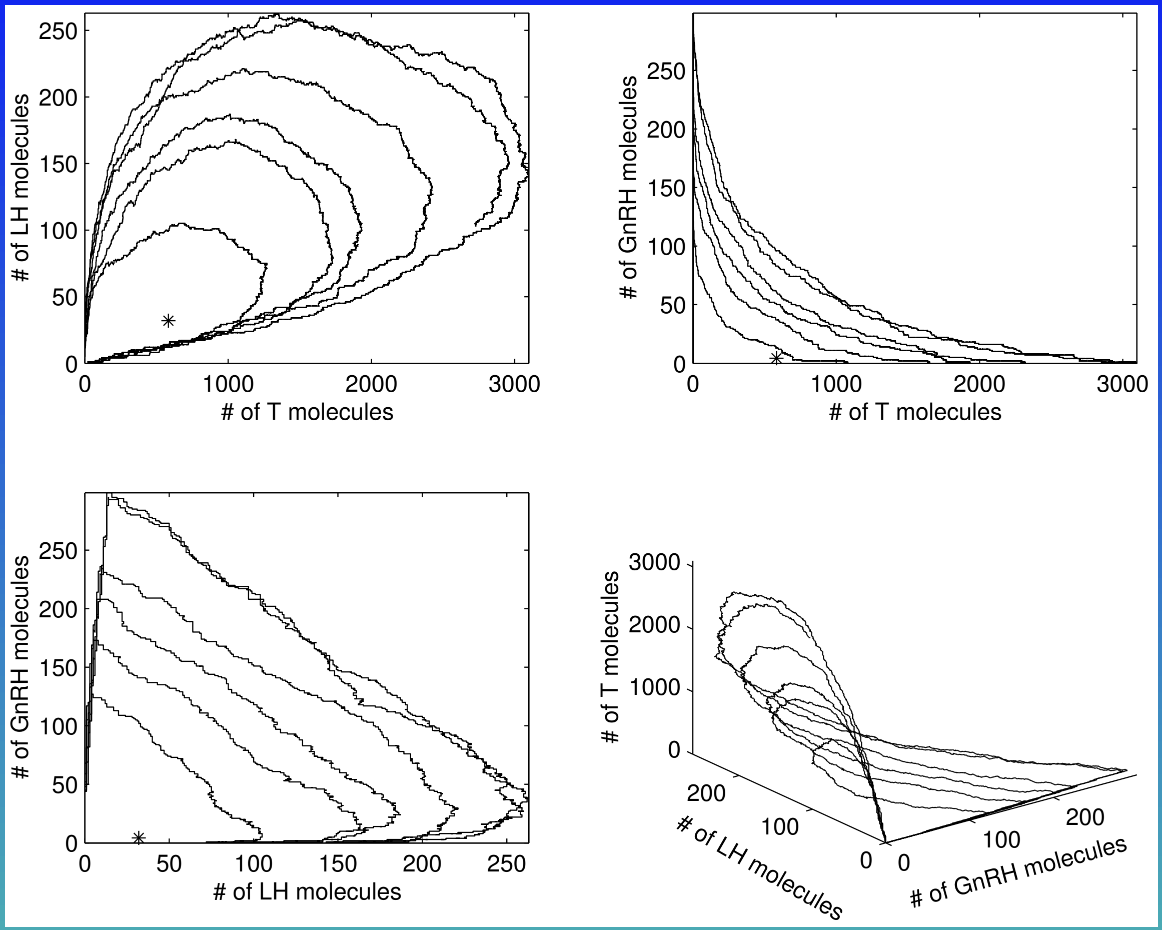
$$a_5 = g_2 L(t) \qquad a_6 = b_3 T(t).$$

A Stochastic Simulation



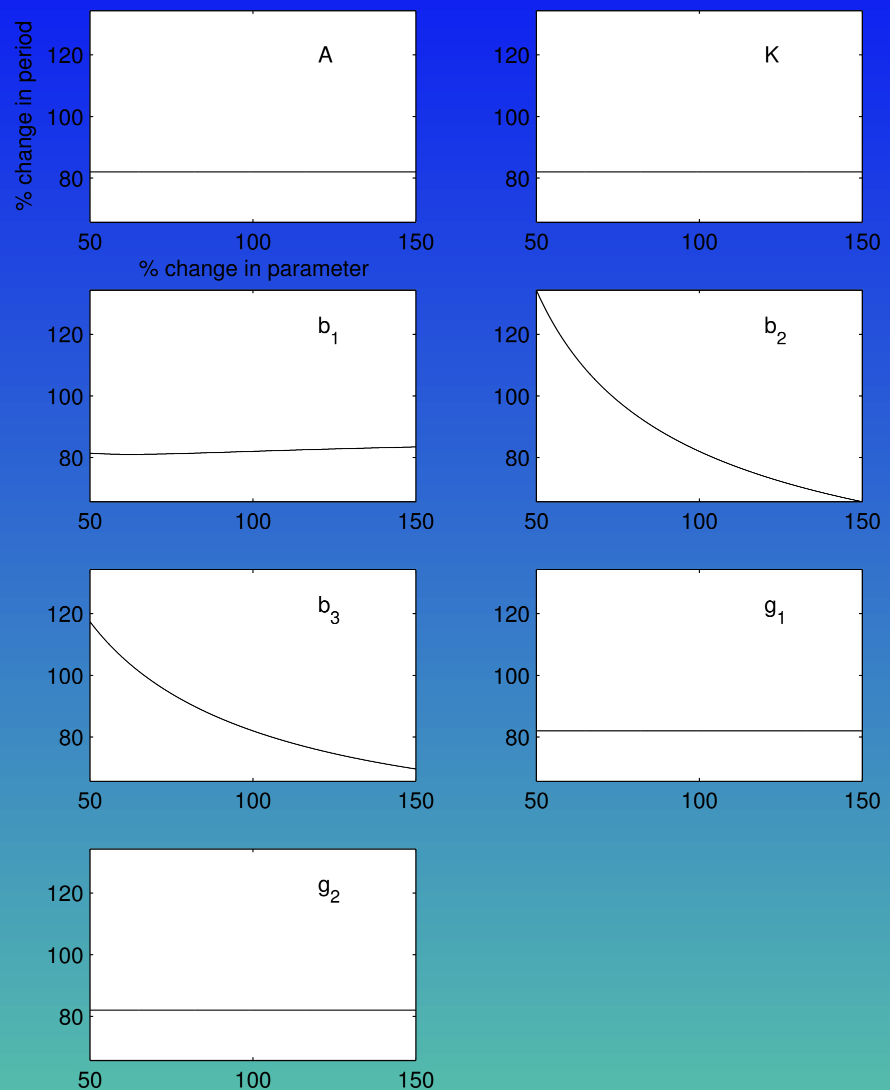
Simulation of hormone secretion for physical parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.032$, $b_3 = 0.046$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by dashed lines; average R is 4.20, average L is 31.90, and average T is 583.44.

A Stochastic Simulation



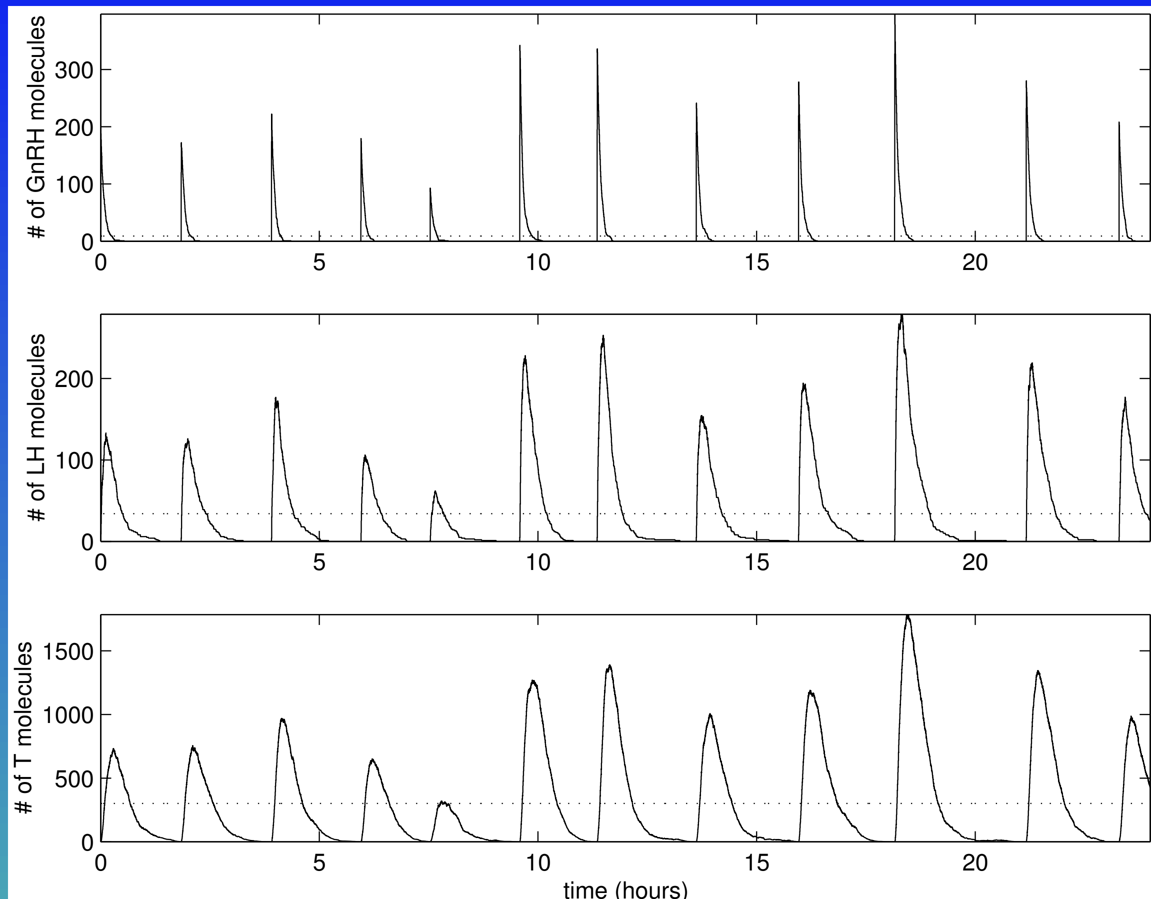
Two dimensional projections and three dimensional plot of simulation trajectory for the physical parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.032$, $b_3 = 0.046$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by asterisks; average R is 4.20, average L is 31.90, and average T is 583.44.

Period Sensitivity Analysis



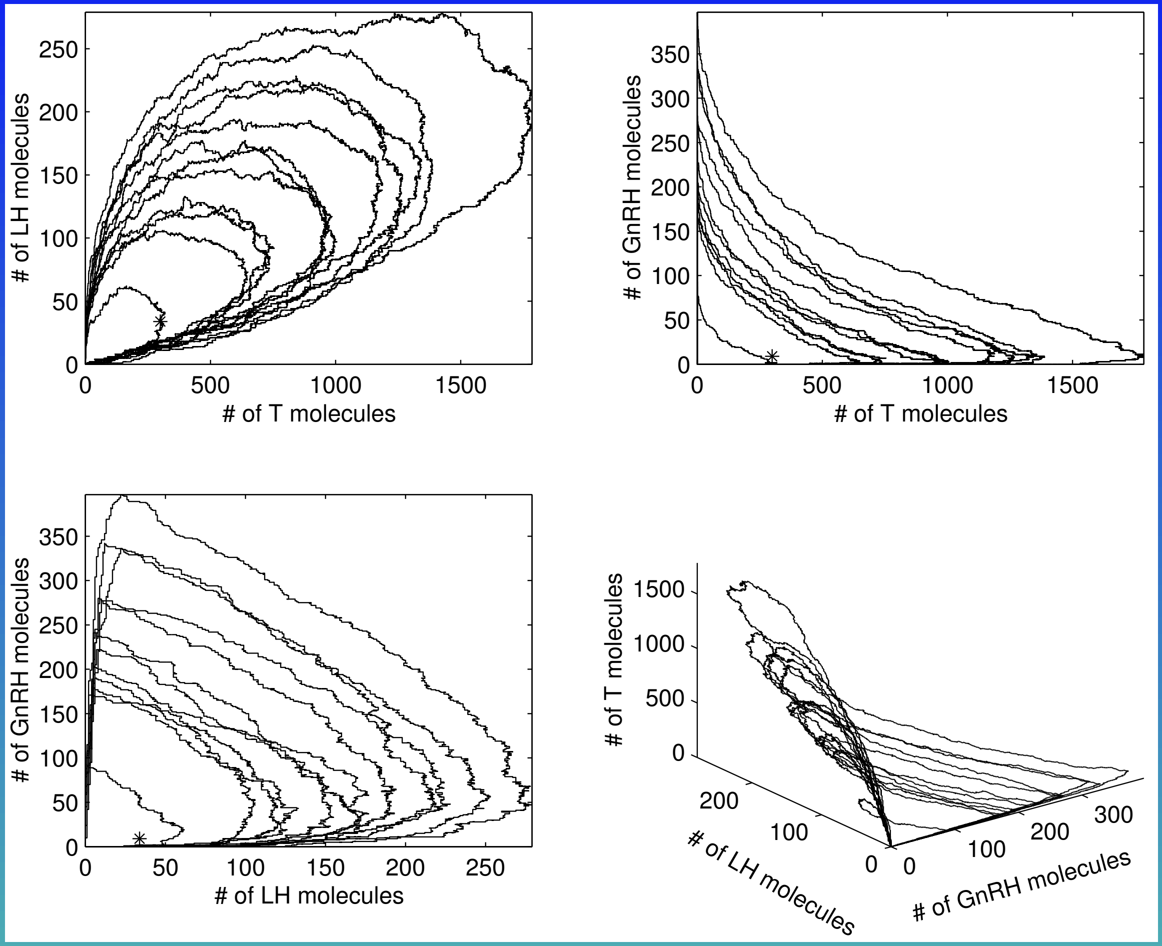
Initial eigenvalues were $\lambda_1 = -0.2385$ and $\lambda_{2,3} = -0.0347 \pm 0.0404i$.

A Stochastic Simulation



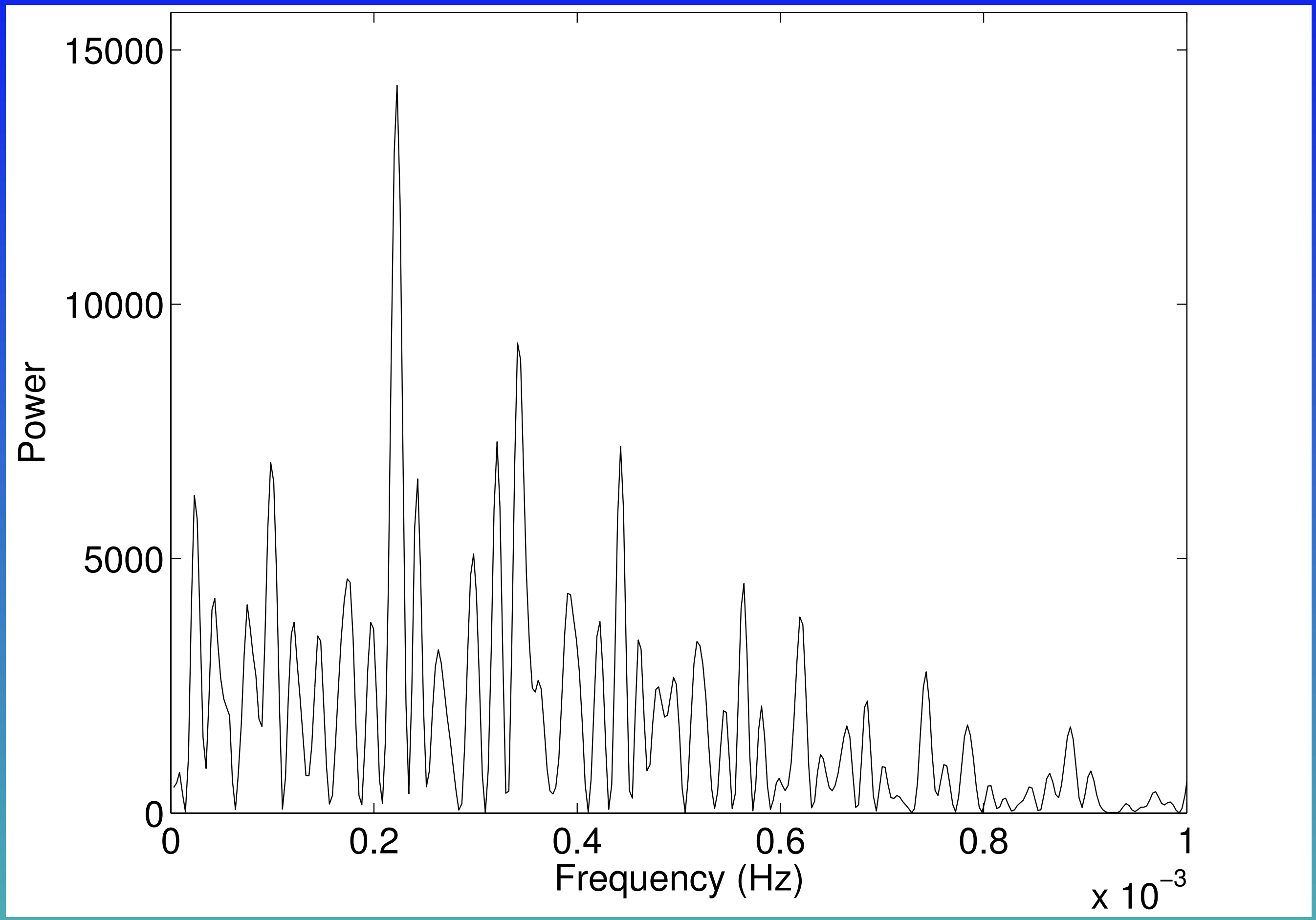
Simulation of hormone secretion for parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.07$, $b_3 = 0.1$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by dashed lines; average R is 9.09, average L is 33.92, and average T is 300.07.

A Stochastic Simulation



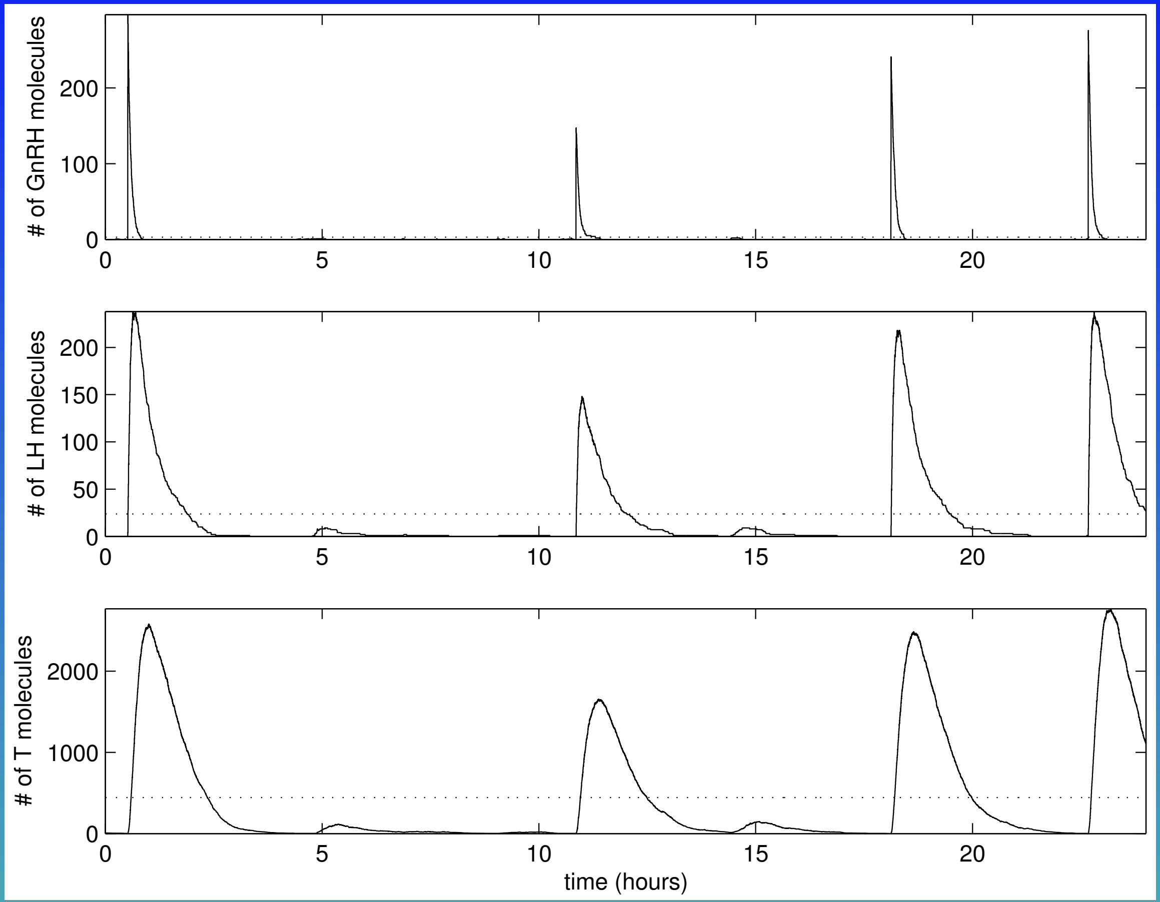
Two dimensional projections and three dimensional plot of simulation trajectory for the physical parameter values, $A = 10^{-4}$, $K = 10^{-7}$, $b_1 = 0.23$, $b_2 = 0.07$, $b_3 = 0.1$, $g_1 = 0.2618$, and $g_2 = 0.9015$. Average number of molecules are represented by asterisks; average R is 9.09, average L is 33.92, and average T is 300.07.

Lomb Spectral Analysis



The largest peak corresponds to a frequency of 2.3429×10^{-4} Hz.

Threshold Phenomenon



Simulation to illustrate the threshold phenomenon. Parameter values are $A = 10^{-1}$, $K = 10^{-4}$, $b_1 = 0.23$, $b_2 = 0.032$, $b_3 = 0.046$, $g_1 = 0.2618$, and $g_2 = 0.9015$.

Analogy to Harmonic Oscillator with Variable Damping

For further discussion of the threshold phenomenon, consider the system of differential equations

$$\frac{dx}{dt} = y$$
$$\frac{dy}{dt} = -\frac{x}{4} - \frac{y}{x^2 + y^2 + 0.1}$$

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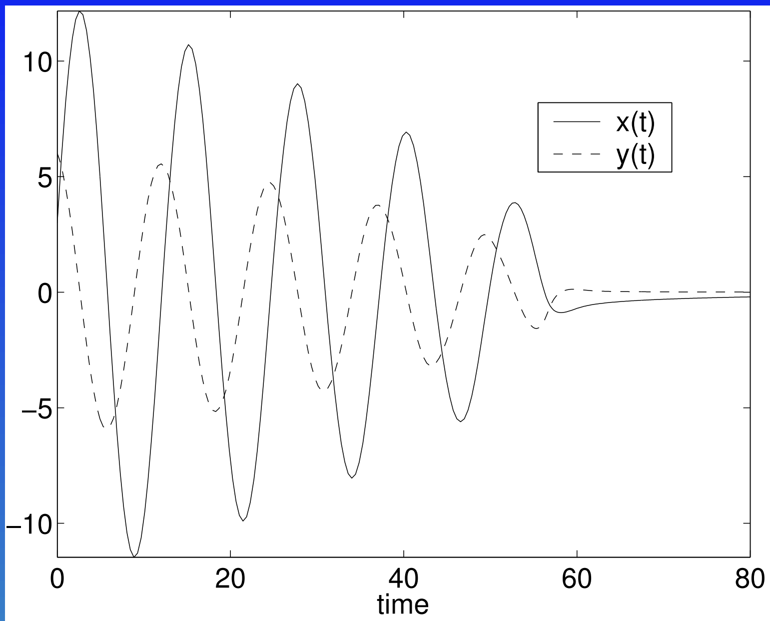
$$\frac{dx}{dt} = y$$
$$\frac{dy}{dt} = -\frac{x}{4} - \frac{y}{x^2 + y^2 + 0.1}$$

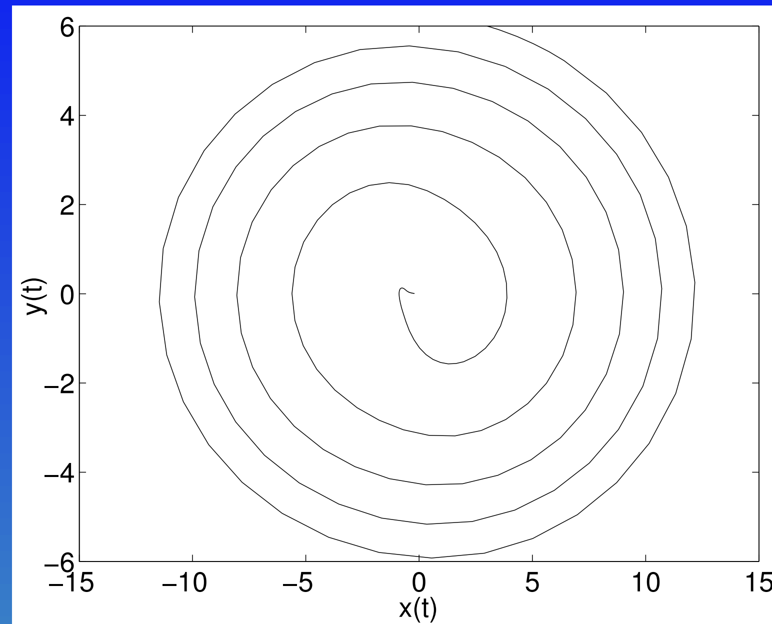
The nullclines of this system are

x-nullcline: $y = 0$

y-nullclines: $y = \dfrac{-2 \pm 2\sqrt{1 - x\left(\frac{x^3}{4} + \frac{x}{40}\right)}}{x}$

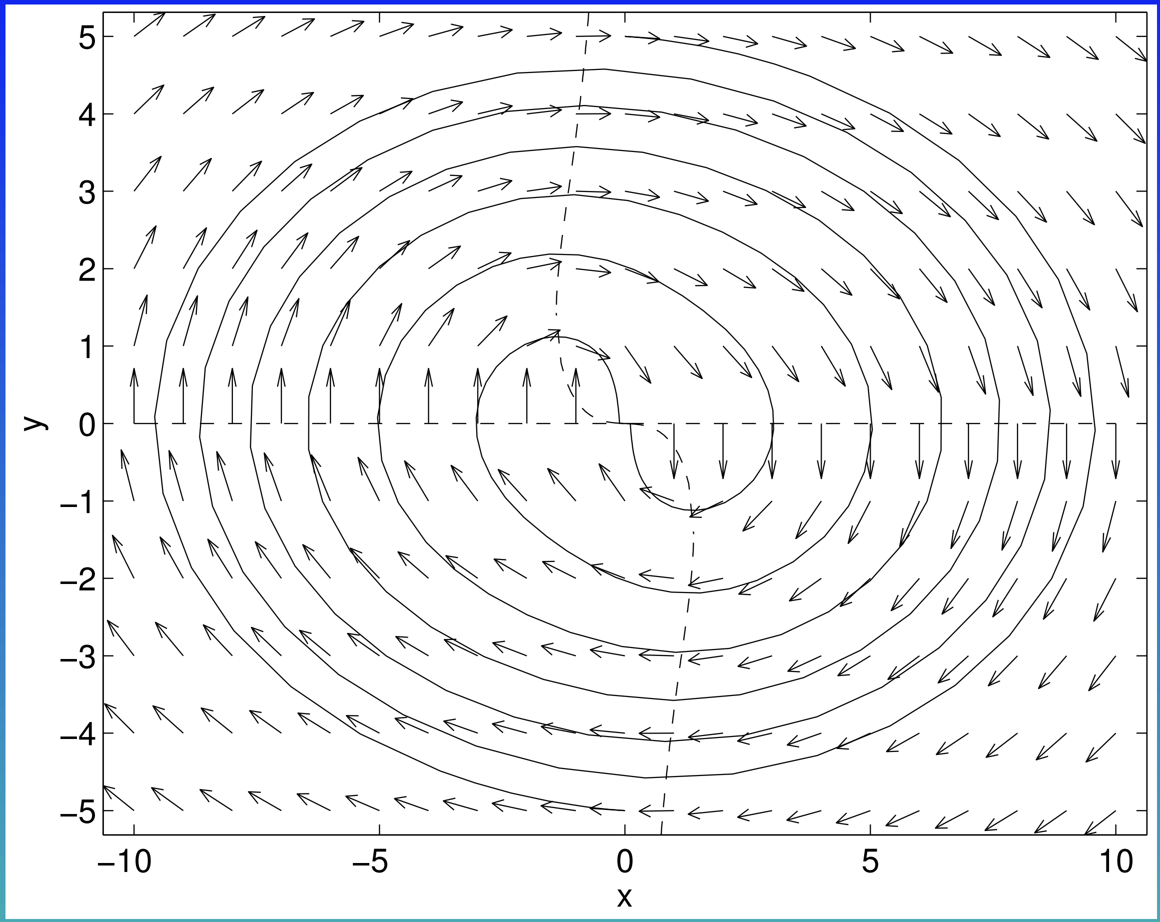
Variable Damping Harmonic Oscillator





Example trajectory and phase curve for the harmonic oscillator with nonlinear damping. Initial conditions are $x(0) = 3$ and $y(0) = 6$.

Variable Damping Phase Portrait



Phase portrait of the harmonic oscillator with nonlinear damping. Initial conditions for the phase curves (solid lines) are $x(0) = 0$ and $y(0) = \pm 5$. The dashed curves are the nullclines for the system.

Variable Damping Threshold Phenomenon

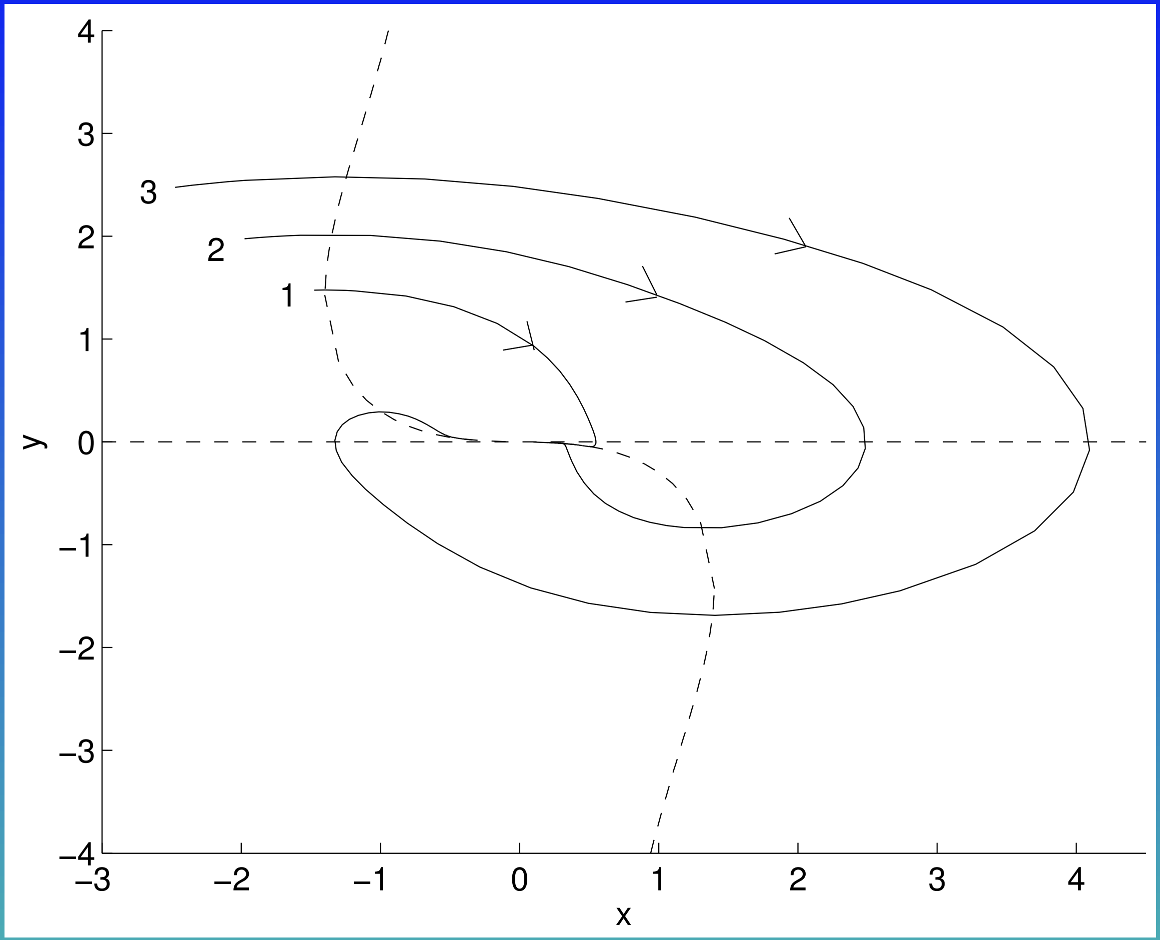


Illustration of the threshold phenomenon for the harmonic oscillator with nonlinear damping. Initial conditions for the phase curves (solid lines) are $(x(0), y(0)) = (-1.5, 1.5)$ for curve 1, $(x(0), y(0)) = (-2, 2)$ for curve 2, and $(x(0), y(0)) = (-2.5, 2.5)$ for curve 3. The dashed curves are the nullclines for the system.

Conclusions

- ⋆ By approaching the hormone model from a different physical basis we saw how intrinsic fluctuations can incite oscillations for low numbers of molecules.
- ⋆ Even though the deterministic model has a globally stable fixed point, the stochastic model was able to capture the pulsatile behavior of the blood hormone levels.
- ⋆ By analogy, we can compare the observed threshold phenomenon to a harmonic oscillator with varying, nonlinear damping.

Future Work

- ⋆ Do a Poincaré-map-like analysis of the oscillations we see with the stochastic model and study the resulting distribution.
- ⋆ Further details can be incorporated into the model, such as basal hormone secretion, temporal shifts, and additional negative feedback relationships in the signaling pathway.
- ⋆ The model can be tested to see if intrinsic fluctuations are still significant when the system has a larger number of molecules or if perhaps extrensic fluctuations could play a role.

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